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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/082,001	02/22/2002	Hans-Ulrich Demuth	20784/6	1724

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EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 12/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/082,001	DEMUTH ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *11-13 and 23-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 14-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10/31/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Oath/Declaration

1. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02. The oath or declaration is defective because non-initialed and/or non-dated alterations have been made to the addresses of inventors, Dagmar Schlenzig and Ulrich Heiser. See 37 CFR 1.52(c).

Election/Restrictions

2. Applicant's election with traverse of Group I, claims 1-10 and 14-22 in the response filed October 20, 2003 is acknowledged. The traversal is on the ground(s) that the claims of Groups I and II are closely related and substantially overlapped, and there will not be a serious burden for examiner to search all the claims. This is not found persuasive because the product of Group I is patentably distinct from the method of Group II as indicated in the restriction requirement. Restriction is proper when two or more claimed inventions are either independent **or** distinct. See MPEP 803. Furthermore, coexamination of each of additional groups would have required a search of additional classes and art areas. For example, if Group II were included, it would require additional searches for class 424, subclasses 94.63 and 9.1, as well as various diseases. Thus, coexamination of each of these inventions would require a serious additional burden of search. Therefore, claims 1-10 and 14-22 are examined in this Office Action.

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of

the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**

Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Claim Objections

3. Claim 14 is objected to because of the formula of B-A-C, where B is not connected to A; and the use of bracketing ([ ]). Bracketing or underlining are commonly used to indicate amendments or changes in the claims as provided in 37 CFR 1.121(a)(2)(ii) and are normally not intended to be printed in the published patent. For example, in claim 14, applicant has used "H-Glu[$NH(CH_2)_7CONH(CH_2)_3NHZ$] pyrrolidide" in such a manner that appears that the instant brackets would indicate deleted material and is thus, confusing as to whether the compound would include "$NH(CH_2)_7CONH(CH_2)_3NHZ$" or not. The applicant can only amend by cancellation and presentation of a new claim. See also changes to 37 CFR 1.121 in Amendment rules package (Final Rule published on 8 Sep. 2000 (65 Fed. Reg. 54603), see also O. G. of 19 Sep. 2000 (1238 Off. Gaz. Pat. Office 77)).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-10 and 14-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a specific B-A-C compound such as glutamylthiazoline of Glu(Gly_3)-Thia, Glu(Gly_5)-Thia or Glu(PEG)-Thia, and a pharmaceutical composition comprising the glutamylthiazoline; or a compound of amino acid pyrrolidide, cyanopyrrolidide or 4-hydroxyproline having amino acid side chain blocked, or a pharmaceutical composition comprising the compound as indicated in the prior art, does not reasonably provide enablement for a compound of the general formula, B-A-C or a pharmaceutical composition comprising the

compound, where the amino acid of A, the sequence of oligopeptide of B, or the substituted organic amine, amide, alcohol, acid or aromatic group of B is not defined. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-10 and 14-22 are directed to a compound of the general formula, B-A-C (claims 1-8) or a pharmaceutical composition (claims 9, 10 and 14-22) comprising the compound, where A is amino acid having a functional group, B is oligopeptide, PEG or organic group having 8-50 carbon atoms. The specification, however, only discloses cursory conclusions (pages 4-6) without data supporting the findings, which state that the present invention provides a compound having a general formula, B-A-C can locally inhibit DP-IV activity. There are no indicia that the present application enables the full scope in view of the compound having a general formula, B-A-C as inhibitors of DP-IV as discussed in the stated rejection. The present application provides no indicia and no teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breath of the claims, the presence of working examples, the state of the prior art and relative skill of those in the art, the unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breath of the claims:

The breath of the claims is broad and encompasses unspecified variants regarding the amino acid of A, the oligopeptide or the organic group of B, which are not adequately described or demonstrated in the specification.

(2). The presence or absence of working examples:

The specification indicates the preparation of specific glutamylthiazoline such as Glu(Gly_3)-Thia, Glu(Gly_5)-Thia or Glu(PEG)-Thia, and the inhibitory activities of these compounds toward serum DP-IV (Examples 1-3). There are no other working examples indicating the claimed variants.

(3). The state of the prior art and relative skill of those in the art:

The prior art (e.g., Jenkins *et al.*, WO-95/15309; Ashworth *et al.*, Bioorg. Med. Chem. Lett. 6, 1163-1166 (1996); Kohn *et al.*, U. S. Patent 6,517,824) teaches the amino acid pyrrolidide, cyanopyrrolidide or 4-hydroxyproline having amino acid side chain blocked with PEG or other organic groups as inhibitors of DP-IV. However, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on the identities of compounds having the formula of B-A-C, and the inhibitory effects of the compound be considered enabling for variants.

(4). Predictability or unpredictability of the art:

The claims encompass various DP-IV inhibitors having the formula of B-A-C, however, identities of the amino acids of A and the oligopeptide or the organic group of B, as well as the effects of the compounds are not sufficiently described in the specification, thus the invention is highly unpredictable regarding the inhibitory effects of the compounds, e.g., Glu(Gly_3)-Thia, Glu(Gly_5)-Thia or Glu(PEG)-Thia, which inhibit DP-IV potently with equal low values of K_I,

inhibit plasma DP-IV quite slowly (Table 1), especially Glu(Gly_5)-Thia, which does not show any systemic action of the orally administered compound, thus the inhibitory effect of the compound is not predictable.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a compound of the general formula, B-A-C or a pharmaceutical composition comprising the compound, where A is amino acid having a functional group, B is oligopeptide, PEG or organic group having 8-50 carbon atoms. The specification indicates a compound having a general formula, B-A-C can locally inhibit DP-IV activity, and Examples 1-3 demonstrate glutamylthiazoline such as Glu(Gly_3)-Thia, Glu(Gly_5)-Thia or Glu(PEG)-Thia, which inhibit DP-IV potently with equal low values of K_I in vitro, inhibit plasma DP-IV quite slowly in rat model (Table 1). The specification further indicate these side chain-modified DP-IV inhibitors may consequently act as basic structures for synthesis of novel topically administered DP-IV inhibitors without systemic action (Example 2). However, the specification has not demonstrated the make/use of various side chain-modified DP-IV inhibitors, nor has indicated the inhibitory effects of these compounds. Moreover, there are no working examples indicating the claimed variants. Since the specification has not provided sufficient teachings on the identities of side chain-modified DP-IV inhibitors, and the effects of the compounds, it is necessary to have additional guidance and to carry out further experimentation to assess the inhibitory effects of various compounds of B-A-C toward DP-IV.

(6). Nature of the Invention

The scope of the claims includes many variants of side chain-modified DP-IV inhibitors, however, the specification has not demonstrated the use and the effects of these variants. Thus, the disclosure is not enabling for reasons discussed above.

In summary, the scope of the claim is broad, while the working example does not demonstrate the claimed variants, the effects of the compound is unpredictable and the teachings in the specification are limited, therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the inhibitory effects of various compounds of B-A-C toward DP-IV.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 14-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Claim 14-22 are indefinite because of the use of the term "C is a group,……..excluding H-Glu[$NH(CH_2)_7CONH(CH_2)_3NHZ$] pyrrolidide……., provided that C is not H-Glu[$NH(CH_2)_7CONH(CH_2)_3NHZ$] pyrrolidide or H-Lys[$CO(CH_2)_3NHSO_2Pfp$] pyrrolidide". The term cited renders the claim indefinite, it is unclear how "C", which is pyrrolidine, can also be implicated as a compound of B-A-C such as H-Glu[$NH(CH_2)_7CONH(CH_2)_3NHZ$] pyrrolidide; and what "Z" or "Pfp" stands for. Claim 14 recites the limitation "the cite of action" in line 18. There is insufficient antecedent basis for this limitation in the claim. Claim 14 is also indefinite as to "the site of action", it is not clear what is the site of action, and how does it affect

the adjuvant, and what is the adjuvant. Claims 15-22 are included in this rejection for being dependent on a rejected claim and not correcting the deficiency of the claim from which they depend.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 14-17, 21 and 22 are rejected under 35 U.S.C. 102(b) as anticipated by Jenkins *et al.* (WO-95/15309).

Jenkins *et al.* disclose various dipeptidyl peptidase IV (DP-IV) inhibitors such as Glu($NH(CH_2)_5COOBn$) pyrrolidide (compound 59 in Table 3) and Glu($NH(CH_2)_5COOBn$) cyanopyrrolidide (compound 97 in Table 3), where the side chain of Glu is covalently linked to a $NH(CH_2)_5COOBn$, which is a substituted amine having 12 carbon atoms; and the inhibitors were tested in Hepes pH 7.8 buffer solution (a pharmaceutically acceptable adjuvant) for their inhibition against DP-IV (pages 9-10; Table 9; claims 14-17, 21 and 22).

8. Claims 14-17, 21 and 22 are rejected under 35 U.S.C. 102(b) as anticipated by Ashworth *et al.* (Bioorg. Med. Chem. Lett. 6, 1163-1166 (1996)).

Ashworth *et al.* disclose a series of DP-IV inhibitors such as Lys(Z)-cyanopyrrolidide (compound 28 in Table II), where the side chain of Lys is covalently linked to Z group

($C_6H_5CH_2OCO$-), which is a substituted aromatic compound having 8 carbon atoms; and the inhibitors were tested in pH 7.4 buffer solution (a pharmaceutically acceptable adjuvant) for their inhibition against DP-IV (Table II, page 1166; claims 14-17, 21 and 22).

9. Claims 1-4, 7, 9, 10, 14-17, 20 and 22 are rejected under 35 U.S.C. 102(e) as anticipated by Kohn *et al.* (U. S. Patent 6,517,824, Filed may 20, 1996).

Kohn *et al.* disclose an antifibrotic composition comprising a copolymer conjugate of L-proline derivative such as poly(PEG-Lys) 4-hydroxyproline (scheme 4b, compound 17; Example 13; claims 1-4), where the side chain amine is covalently linked to PEG having molecular weight from about 500 to about 15,000 (column 4, lines 59-63; claims 7 and 20), and a pharmaceutically acceptable carrier including diluents, solubilizer, enhancers and buffers (column 5, lines 46-64; column 8, lines 9-21; claims 9, 10, 14-17 and 22).

Conclusion

10. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (703) 308-9437. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D. CMK
Patent Examiner

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December 8, 2003

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